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Original article

Elevated plasma brain natriuretic peptide levels predict left atrial appendage dysfunction in patients with acute ischemic stroke

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ABSTRACT

Background: It is well known that left atrial appendage (LAA) dysfunction plays an important role in the occurrence of cardioembolic stroke. The atrium is the main source of brain natriuretic peptide (BNP) in patients with atrial fibrillation (AF). We hypothesized that the plasma BNP level would be a sensitive predictor of LAA dysfunction in patients with acute ischemic stroke.

Methods and results: Transesophageal echocardiography was performed and plasma BNP levels were measured in 223 patients (145 males, age 69 ± 14 years), within 7 days after the onset of acute ischemic stroke. None of the patients had a history of congestive heart failure. LAA thrombus was detected in 23 of 77 (30%) patients with AF. Plasma BNP levels were markedly higher in patients with cardioembolic stroke compared to those without (144 pg/ml vs. 35 pg/ml, $p < 0.05$). Plasma BNP levels were significantly correlated with LAA emptying flow velocity regardless of sinus rhythm ($R = -0.352$) or AF ($R = -0.436$). Furthermore, among patients with cardioembolic stroke, plasma BNP levels were markedly higher in patients with cardiogenic stroke, as diagnosed by transesophageal echocardiography, than in those with cryptogenic stroke (193 pg/ml vs. 14 pg/ml, $p < 0.05$). Multivariate logistic regression analysis showed that a BNP concentration >90 pg/ml was an independent predictor of cardiogenic stroke (odds ratio 41.39, 95% confidence interval 1.28–138; $p = 0.0358$).

Conclusion: Elevated plasma BNP concentrations may be a reliable surrogate marker for the prediction of LAA dysfunction and cardiogenic stroke in patients with acute ischemic stroke.

Introduction

The National Institute of Neurological Disorders and Stroke (NINDS) has characterized cardioembolic stroke as an important clinical issue, because it is the most common cause of death in patients with acute ischemic stroke [1,2]. It is well known that the left atrial appendage (LAA) is a major source of thromboembolism in stroke patients with atrial fibrillation (AF) [3–6]. Many clinical studies have shown a close relationship between LAA thrombus formation and left atrial mechanical remodeling, based on findings from transesophageal echocardiography (TEE) [7,8]. It was reported that the presence of spontaneous echocardiographic contrast (SEC) or measurement of LAA peak flow velocity (LAA eV) by TEE is useful for the detection of LAA dysfunction, which causes LAA thrombus formation [9,10]. However, TEE is a semi-invasive procedure and therefore cannot be used as a screening tool to quantify the risk of stroke in patients with AF.

Brain natriuretic peptide (BNP) levels increase in patients with heart disease [11–13], and it has been used as a marker that is produced by the heart. Plasma BNP is frequently elevated after acute ischemic stroke [14,15] and it has been shown to be an independent predictor of mortality in stroke patients [16]. Many studies have demonstrated that BNP is secreted mainly from the ventricular myocardium [17]. However, it was also reported that the left atrium is the main source of BNP in patients with AF [13]. Recent reports have suggested an association between plasma BNP levels and cardioembolic stroke [18,19]. However, it is not known whether plasma BNP levels are associated with LAA function as evaluated by TEE. We hypothesized that elevated BNP levels are associated with LAA dysfunction, which causes LAA thrombus

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formation in patients with acute ischemic stroke. In the present study, plasma BNP levels were compared with conventional markers of LAA dysfunction, and the feasibility of plasma BNP level as a predictor of LAA dysfunction and cardioembolic stroke in patients with acute ischemic stroke was investigated.

Methods

Study patients

Transthoracic echocardiography (TTE) and TEE were performed in 223 consecutive patients referred to our department of neurosurgery for the treatment of acute cerebral infarction from April 2005 to January 2010. TTE and TEE were performed within 7 (6 ± 1) days of onset. The following patients were excluded: those with structural heart diseases such as ischemic cardiomyopathy ($n = 9$), dilated cardiomyopathy ($n = 4$), hypertrophic cardiomyopathy ($n = 2$), or valvular heart disease ($n = 8$), and those in whom TEE failed ($n = 3$). We defined ischemic cardiomyopathy as having prior myocardial infarction and left ventricular wall motion asynergy. Assessment at admission included determination of the risk factors for cerebral infarction, the clinical ischemic stroke category (NINDS) [20], and disease severity, as assessed using the US National Institute of Health Stroke Scale (NIHSS) [1]. Patients with no history of AF and no documented AF on continuous electrocardographic (ECG) monitoring during hospitalization were categorized as patients with sinus rhythm. Patients with a history of AF prior to admission and/or documented AF on continuous ECG monitoring during hospitalization were categorized as patients with chronic AF.

According to NINDS clinical categories, the findings of computed tomography, magnetic resonance imaging, and TEE, patients were categorized into two groups based on the incidence of cardioembolic stroke (non-cardioembolic stroke: $n = 154$, mean age 67 ± 14 years; cardioembolic stroke: $n = 69$, mean age 72 ± 13 years). Since cardioembolic stroke includes cardiogenic and cryptogenic stroke, we further divided patients with cardioembolic stroke into those with cardiogenic stroke and those with cryptogenic stroke based on the TEE findings. Patients with cardiogenic stroke were defined as those in whom intracardiac thrombi and/or severe LAA dysfunction (severe or moderate SEC and/or LAA eV < 20 cm/s) were detected by TEE ($n = 51$). Patients with cryptogenic stroke were defined as those in whom normal LAA function and atrial septal aneurysm (ASA) and/or patent foramen ovale (PFO) were detected by TEE ($n = 18$). Patient characteristics, echocardiographic parameters, and plasma BNP levels were compared between non-cardioembolic stroke and cardioembolic stroke. The study protocol was approved by the local ethics committee, and all subjects gave informed consent.

Echocardiography

TTE was performed on a Hewlett Packard SONOS 7500 ultrasound instrument (Hewlett Packard, Palo Alto, CA, USA), equipped with a sector transducer. A 5 MHz phased-array multiplane probe was used for TEE. The following parameters were assessed using standard views and techniques [21]: left atrial dimension (LAD), left ventricular end-diastolic dimension (LVDd), left ventricular percent fractional shortening (LVFS), the ratio of peak early to late filling velocity (E/A), deceleration time of early diastolic filling (DCT), and the ratio of peak early mitral annular velocity to E wave (E/E') as measured by TTE. The tissue Doppler velocities were measured at the lateral annulus by using spectral Doppler tissue imaging. The severity of SEC was defined according to the criteria of Fatkin et al., and was graded from 0 to 4+, with grades 3+ and 4+ being defined as SEC [22]. ASA was defined as protrusion of the septum, or a portion of it, at least 10 mm into the left or right atrium [23]. PFO was assessed at rest and during the Valsalva maneuver, with intravenous injection of agitated saline. PFO was diagnosed when at least four microbubbles passed through the septum into the left atrium, either spontaneously or during the Valsalva maneuver [24]. LAA thrombus was diagnosed when a fixed or mobile echogenic mass could be clearly differentiated from the wall of the left atrium or atrial appendage. LAA eV was measured using pulsed wave Doppler, with the sample volume placed 1 cm distal from the mouth of the appendage by TEE. Peak flow velocity within each RR interval was obtained by scanning the appendage at angles between 0° and 90° [25]. In patients with AF, echocardiographic measurements were obtained as the mean of five consecutive cardiac cycles, and in patients with sinus rhythm, as the mean of three consecutive cardiac cycles. All findings were evaluated by two independent experienced echo-cardiologists, who were blinded to the clinical and other details of the patients. We defined LAA dysfunction as LAA eV < 20 cm/s and/or which was the severity of SEC grade 3+ or 4+ [9,22].

Hemostatic markers

Venous blood samples were collected at the time of the echocardiographic studies for determination of plasma BNP levels and serum hemostatic marker levels. Plasma BNP levels were measured using a commercially available specific radioimmunoassay (Shiono RIA BNP assay kit, Shionogi Co. Ltd., Tokyo, Japan) [26]. Other parameters were measured by routine laboratory methods.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) for continuous variables and as percentages of the total number of patients for categorical variables. Skewed variables are presented as medians with interquartile range. Statistical analyses were performed using StatView, version 5.0 (SAS Institute Inc., Cary, NC, USA). *t*-tests and chi-square tests were used for comparison of continuous and categorical variables, respectively. If data were not normally distributed, the Mann–Whitney *U* test was used. Comparisons among three or more groups were performed by analysis of variance (ANOVA) with the Bonferroni post hoc test. *p*-Values <0.05 were considered significant. A receiver operating characteristic (ROC) curve was constructed to determine the relevant plasma BNP cut-off value giving optimum sensitivity and specificity for predicting cardiogenic stroke. The area under the curve was calculated by the trapezoidal rule. Logistic regression analysis was performed to identify independent predictors of the prevalence of cardiogenic stroke among all patients. Variables that were significant by univariate logistic regression analysis ($p < 0.05$) were entered into the multivariate analysis.

Results

The clinical characteristics of the patients with or without cardioembolic stroke are compared in Table 1. Patients with cardioembolic stroke were significantly older, had higher heart rates, and higher CHADS2 scores. The prevalence of AF was higher in patients with cardioembolic stroke than in those with non-cardioembolic stroke. Patients with cardioembolic stroke had a significantly larger LAD, larger LVDd, smaller LVFS, larger E/A (measured in patients with sinus rhythm), larger E/E', and a smaller LAA eV compared to those without. The prevalence of LAA thrombus and SEC was significantly greater in patients with cardioembolic stroke than in those without. Plasma BNP was significantly higher in patients with cardioembolic stroke than in those without. Furthermore, among patients with cardioembolic stroke, plasma BNP

Table 1
Comparison of clinical characteristics between patients with and without cardioembolic stroke.

	Non-cardioembolic ($n=154$)	Cardioembolic ($n=69$)	p-Value
Age (years)	67 ± 14	72 ± 13	0.0065
Gender (M/F)	104/50	41/28	0.2403
Heart rate (bpm)	69 ± 13	78 ± 16	<0.0001
Atrial fibrillation	29 (19%)	48 (70%)	<0.0001
Hypertension	113 (73%)	48 (70%)	0.5570
Diabetes mellitus	44 (29%)	19 (28%)	0.8739
Hyperlipidemia	87 (56%)	19 (28%)	<0.0001
Current smoking	90 (58%)	33 (48%)	0.1406
Previous stroke	43 (27%)	18 (27%)	0.5992
NIHSS	4.6 ± 5.2	5.1 ± 5.9	0.5328
CHADS2 score	1.4 ± 1.0	1.9 ± 1.3	0.0012
Medication			
Antiplatelets	90 (58%)	22 (31%)	0.0105
Anticoagulants	15 (10%)	25 (36%)	<0.0001
PT-INR	1.59 ± 0.51	1.68 ± 0.53	0.5964
Echocardiography			
LAD (mm)	37 ± 6	43 ± 6	<0.0001
LVDd (mm)	47 ± 5	48 ± 6	0.0444
LVFS (%)	36 ± 7	33 ± 8	0.0005
LAA eV (cm/s)	53 ± 22	30 ± 27	<0.0001
SEC	6 (4%)	34 (49%)	<0.0001
LAA thrombus	0 (0%)	27 (39%)	<0.0001
E/A (sinus rhythm)	0.84 ± 0.34	1.05 ± 0.51	0.0073
Deceleration time	206 ± 48	199 ± 91	0.3865
E/E'	7.5 ± 2.4	9.7 ± 4.8	0.0041
Aortic plaque	35 (22%)	3 (5%)	0.0172
Carotid plaque	34 (22%)	7 (11%)	0.0518
Blood marker			
BNP (pg/ml)	35 (13–85)	144 (61–274)	<0.0001
Fibrinogen (mg/dl)	395 ± 132	485 ± 193	<0.0001
D-dimer (mg/ml)	1.0 (0.5–2.8)	2.0 (0.7–3.5)	0.0196
FDP (mg/ml)	3.8 (2.8–6.0)	4.8 (3.5–7.9)	0.0065

Date are expressed as mean ± SD, as number (percentage), or as median (interquartile range). NIHSS, National Institutes of Health Stroke Scale; CHADS2, an acronym for Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack; PT-INR, prothrombin time-international normalized ratio; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVFS, left ventricular percent fractional shortening; LAA eV, left atrial appendage emptying flow velocity at atrial systole; SEC, spontaneous echo contrast; E/A, the ratio of peak early to late filling velocity; E/E', the ratio of peak early mitral annular velocity to E wave; Aortic plaque, protruding >5 mm and/or mobile plaques in the aortic arch; Carotid plaque, protruding plaque with 50% luminal stenosis in the common and/or proximal internal carotid artery; BNP, brain natriuretic peptide; FDP, fibrinogen degradation products.

levels were significantly higher in patients with cardiogenic stroke than in those with cryptogenic stroke (Fig. 1).

The patients were classified into three groups based on LAA eV and the prevalence of LAA thrombus. Patients with LAA thrombus had significantly higher BNP levels compared to those without LAA thrombus (Fig. 2A). Despite the absence of LAA thrombus, patients with low LAA eV had higher BNP levels compared to those with high LAA eV (Fig. 2A). Irrespective of cardiac rhythm, plasma BNP levels were higher in patients with LAA thrombus than in those without LAA thrombus (Fig. 2B). Plasma BNP levels were significantly correlated with LAA eV regardless of their cardiac rhythm (Fig. 3A,B). Even in 88 patients with preserved LV systolic (LVFS >35%) and diastolic function ($E/E' < 10$), plasma BNP levels were significantly correlated with LAA eV ($R = 0.325$, $p < 0.05$).

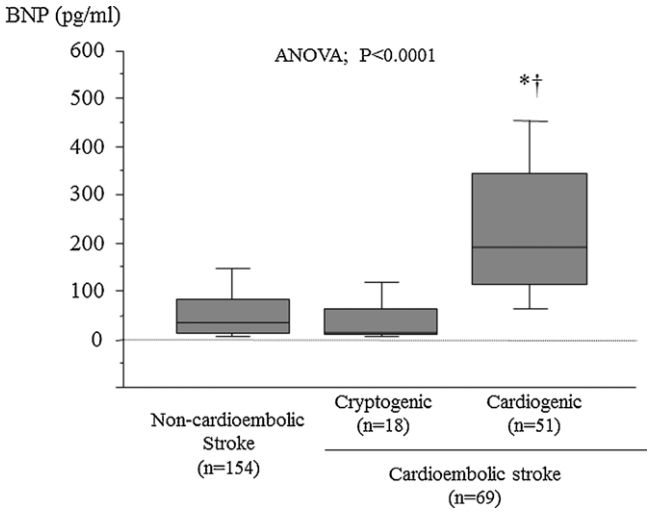

Fig. 1. Comparison of plasma brain natriuretic peptide (BNP) levels among patients with non-cardioembolic, cryptogenic, and cardiogenic stroke. *$p < 0.01$ versus non-cardioembolic stroke; †$p < 0.01$ versus cryptogenic stroke. ANOVA, analysis of variance.

The optimum plasma BNP cut-off value for predicting cardiogenic stroke (cardioembolic stroke excluding cryptogenic stroke) was determined as that which gave the greatest sum of sensitivity plus specificity on the ROC curve. The ROC curve for plasma BNP as a predictor for cardiogenic stroke is shown in Fig. 4. The area under the ROC curve (AUC) was 0.892. For a BNP level >90 pg/ml the sensitivity was 85% and the specificity was 78%. Therefore, we determined that the cut-off value of BNP for predicting cardiogenic stroke is 90 pg/ml. As shown in Fig. 5, patients with high BNP level had high prevalence of LAA thrombus independently of CHADS2 score. No patients with CHADS2 score <2 and BNP ≤ 90 pg/ml had LAA thrombus.

The incidence of AF and cardioembolic stroke, and CHADS2 scores were significantly higher in patients with high BNP levels (>90 pg/ml) than in those with low BNP levels (Table 2). Patients with high BNP levels had a significantly larger LAD, smaller LVFS, higher E/A, higher E/E', and lower LAA eV compared to those with low BNP levels. Patients with high BNP levels had a significantly higher prevalence of SEC and LAA thrombus compared to those with low BNP levels.

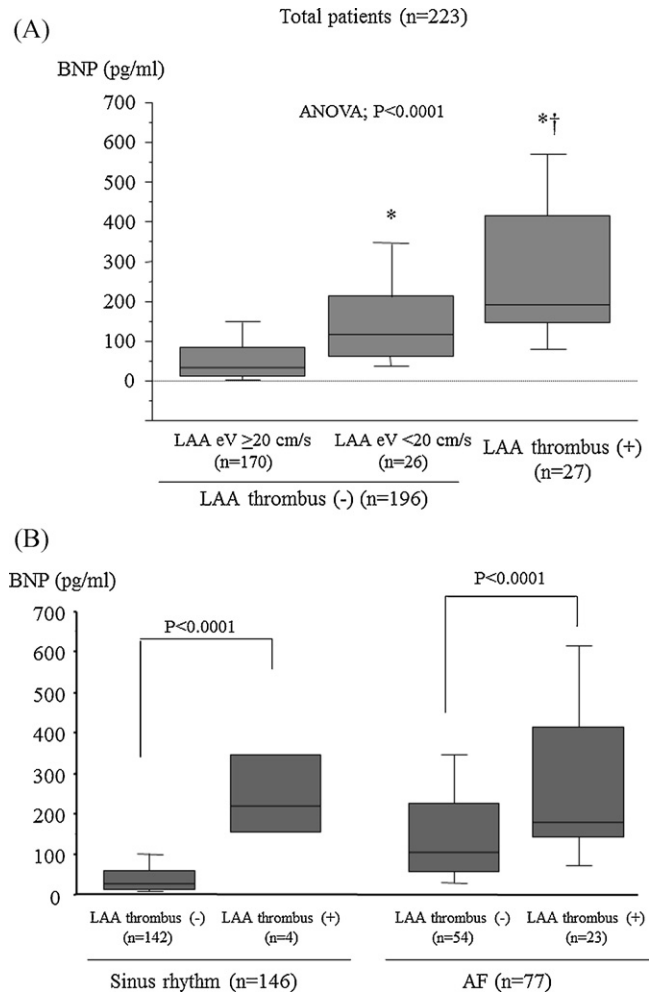

Fig. 2. (A) Comparison of plasma BNP levels among patients with high LAA eV, low LAA eV, and LAA thrombus. $^{*}p < 0.01$ versus LAA eV ≥ 20 cm/s; $^{\dagger}p < 0.01$ versus LAA eV ≤ 20 cm/s. (B) Comparison of plasma BNP levels between patients with or without LAA thrombus. AF, atrial fibrillation; ANOVA, analysis of variance; BNP, brain natriuretic peptide; LAA eV, left atrial appendage emptying flow velocity.

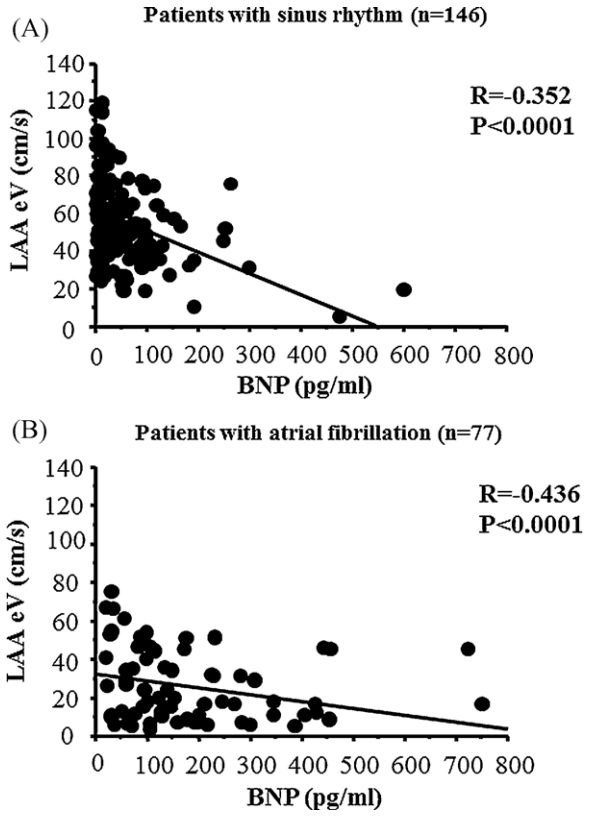

Fig. 3. Relationship between plasma BNP level and LAA eV in patients with sinus rhythm (A) and atrial fibrillation (B). BNP, brain natriuretic peptide; LAA eV, left atrial appendage emptying flow velocity.

Logistic regression analysis was performed to identify independent predictors of cardiogenic stroke (Table 3). In the univariate logistic regression analysis, age, CHADS2 score, LAD, LVFS, LAA eV, *E*/*A*, *E*/*E*′, fibrinogen, BNP >90 pg/ml, and the presence of AF, hyperlipidemia, SEC, and LAA thrombus were significantly associated with cardiogenic stroke. In the multivariate logistic regression analysis, the presence of AF and BNP >90 pg/ml was independent predictor of cardiogenic stroke (Table 3).

Discussion

It was reported that the left atrium is the main source of BNP in patients with AF [13]. Ari et al. reported that plasma BNP was useful as a predictor of the recurrence of AF after cardioversion and maintenance of sinus rhythm [27]. The present study showed that there was a significant correlation between plasma BNP levels and parameters of LAA function such as LAA eV. Furthermore, the ROC curve demonstrated that plasma BNP showed good sensitivity and specificity for predicting cardiogenic stroke. We determined that the cut-off value of BNP for predicting cardiogenic stroke is 90 pg/ml. We are convinced that this cut-off value may become the noninvasive diagnostic tool for cardiogenic stroke, and that it is useful to decide initiating early anticoagulant therapy for cardiogenic stroke without waiting for TEE findings.

The present study showed that plasma BNP levels were associated with LAA function, independently of cardiac rhythm (Fig. 3). BNP is secreted into the plasma mainly in response to mechanical stretching of the LV myocardium. In the present study, patients with high plasma BNP levels had a higher *E*/*E*′ and left atrial volume index and smaller LVFS compared to those with low plasma BNP

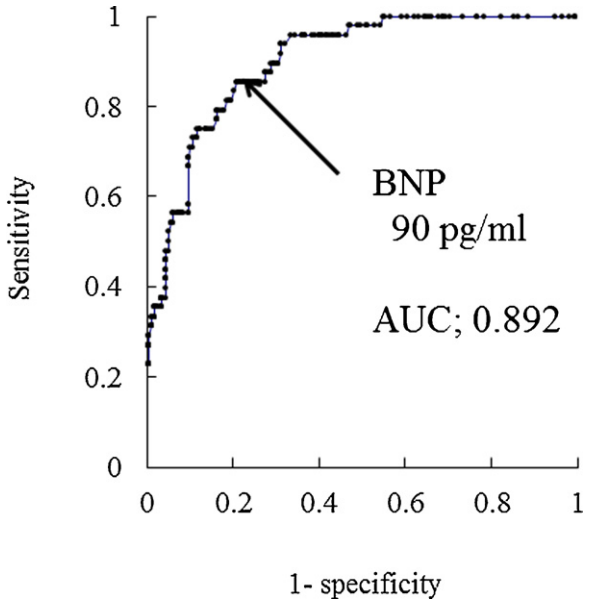

Fig. 4. The ROC curve analysis for plasma BNP as a predictor of cardiogenic stroke. AUC, area under the curve; ROC, receiver operating characteristic; BNP, brain natriuretic peptide.

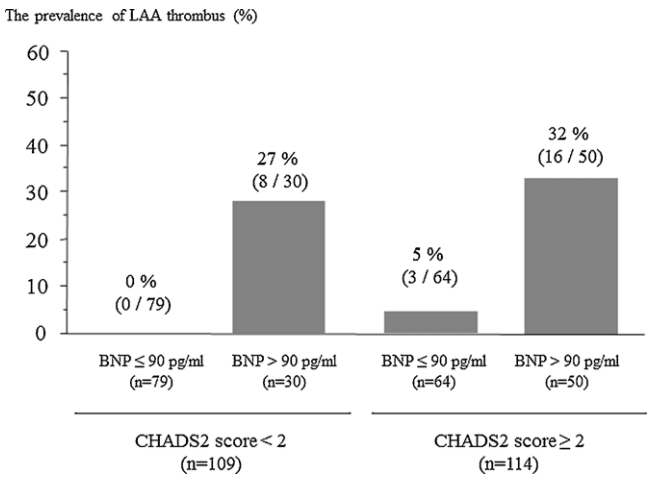

Fig. 5. The association of CHADS2 score with plasma BNP levels. BNP, brain natriuretic peptide; LAA, left atrial appendage.

levels. These results suggest that BNP is secreted by both LA and LV myocardium. The LA is exposed to high LV filling pressures caused by LV systolic and diastolic dysfunction, and the long-term increase in LV filling pressure leads to LA dilatation and LAA dysfunction. In the present study, even in patients with preserved LV systolic and diastolic function, plasma BNP levels were significantly correlated with LAA eV. This result suggests that high BNP levels may reflect the potential LAA dysfunction and preserved LV systolic and diastolic function.

Patients with high CHADS2 score have been shown to have a high incidence of ischemic stroke, despite receiving warfarin [28]. The present study demonstrated that patients with high BNP levels had higher prevalence of LAA thrombus independently of CHADS2 score compared to those with low BNP levels (Fig. 5). This result suggested that plasma BNP levels provide important additional information for LAA dysfunction and/or LAA thrombus formation. Further, BNP levels could successfully differentiate cardiogenic stroke from cryptogenic stroke (Fig. 1). It is well known that cryptogenic stroke occurs mainly due to deep venous thrombus in patients with ASA and/or PFO [29]. These results suggest that elevated plasma BNP levels are associated with LAA dysfunction rather than the presence of thrombus itself. Some previous studies have shown a relationship between plasma BNP levels and cardioembolic stroke. Shibazaki et al. reported that elevated plasma BNP (>140 pg/ml) was a useful marker for the diagnosis of cardioembolic stroke in patients with acute ischemic stroke [18]. However, they did not elucidate the mechanism by which BNP was increased in cardioembolic stroke as they did not perform TEE. Since the proportion of patients with cardioembolic stroke enrolled in that study (41%) was greater than in the present study (21%), the cut-off values for plasma BNP were higher in that study. Di Angelantonio et al.

Table 2
Comparison of clinical characteristics between patients with high BNP and low BNP.

	BNP ≤90 pg/ml (n = 143)	BNP >90 pg/ml (n = 80)	p-Value
Age (years)	66 ± 14	73 ± 12	0.0003
Gender (M/F)	93/50	52/28	0.9700
Heart rate (bpm)	71 ± 14	74 ± 17	0.1606
Atrial fibrillation	25 (17%)	53 (66%)	<0.0001
Hypertension	98 (69%)	63 (79%)	0.1023
Diabetes mellitus	37 (26%)	26 (35%)	0.2918
Hyperlipidemia	77 (54%)	29 (36%)	0.0116
Current smoking	81 (57%)	42 (53%)	0.5507
Previous stroke	38 (27%)	23 (29%)	0.7477
NIHSS	4.4 ± 5.0	5.5 ± 6.1	0.1501
CHADS2 score	1.4 ± 1.0	1.9 ± 1.2	0.0001
NINDS clinical categories			<0.0001
Cardioembolic stroke	21 (15%)	48 (60%)	
Atherothrombotic stroke	54 (38%)	16 (20%)	
Lacunar stroke	27 (19%)	4 (8%)	
Others or Undetermined	41 (29%)	12 (15%)	
Medication			
Anti platelets	79 (55%)	33 (41%)	0.0955
Anti coagulants	18 (13%)	22 (28%)	0.0054
PT-INR	1.63 ± 0.46	1.66 ± 0.58	0.8603
Echocardiography			
LAD (mm)	37 ± 6	42 ± 6	<0.0001
LVDd (mm)	47 ± 5	48 ± 6	0.6207
LVFS (%)	37 ± 6	33 ± 8	<0.0001
LAA eV (cm/s)	54 ± 24	32 ± 21	<0.0001
SEC	10 (7%)	30 (38%)	<0.0001
LAA thrombus	3 (2%)	24 (30%)	<0.0001
E/A (sinus rhythm)	0.83 ± 0.33	1.02 ± 0.48	0.0063
Deceleration time	210 ± 47	195 ± 86	0.0961
E/E'	7.1 ± 2.4	10.2 ± 4.4	<0.0001
Aortic plaque	24 (17%)	14 (18%)	0.2138
Carotid plaque	31 (22%)	10 (13%)	0.0897
Blood marker			
BNP (pg/ml)	26 (10–51)	172 (115–269)	<0.0001
Fibrinogen (mg/dl)	388 ± 129	485 ± 185	<0.0001
D-dimer (mg/ml)	0.8 (0.5–2.5)	2.0 (0.8–4.3)	0.0005
FDP (mg/ml)	3.8 (2.7–5.7)	4.8 (3.4–8.5)	0.0021

BNP, brain natriuretic peptide; NIHSS, National Institutes of Health Stroke Scale; CHADS2, an acronym for Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack; PT-INR, prothrombin time-international normalized ratio; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVFS, left ventricular percent fractional shortening; LAA eV, left atrial appendage emptying flow velocity at atrial systole; SEC, spontaneous echo contrast; E/A, the ratio of peak early to late filling velocity; E/E', the ratio of peak early mitral annular velocity to E wave; Aortic plaque, protruding >5 mm and/or mobile plaques in the aortic arch; Carotid plaque, protruding plaque with 50% luminal stenosis in the common and/or proximal internal carotid artery; FDP, fibrinogen degradation products.

Table 3
Univariate and multivariate logistic regression analyses for cardiogenic stroke.

Variables		Risk ratio	95% CI	*p*-value
Univariate analysis				
Age	(per 1 year increase)	1.073	1.033–1.155	0.0003
Atrial fibrillation		60.97	17.77–209.2	<0.0001
Hyperlipidemia		0.206	0.096–0.443	<0.0001
CHADS2 score	(per 1 SD increase)	1.610	1.610–2.232	0.0042
LAD (mm)	(per 1 SD increase)	7.020	3.797–12.96	<0.0001
LVFS (%)	(per 1 SD decrease)	1.905	1.350–2.674	<0.0001
LAA eV (cm/s)	(per 1SD decrease)	15.14	6.835–33.47	<0.0001
SEC		33.96	13.47–85.67	<0.0001
LAA thrombus		51.33	14.34–183.7	<0.0001
E/*A*	(per 1SD increase)	3.342	1.768–6.317	0.0002
E/*E*′	(per 1SD increase)	2.716	1.354–5.556	0.0062
Fibrinogen (mg/dl)	(per 1 SD increase)	2.232	1.619–3.606	0.0042
BNP >90 pg/ml		21.19	8.727–51.45	<0.0001
Multivariate analysis				
Age	(per 1 year increase)	0.949	0.799–1.126	0.5482
Atrial fibrillation		47.18	1.789–1244	0.0210
CHADS2 score	(per 1 SD increase)	0.631	0.168–2.372	0.4960
LAD (mm)	(per 1 SD increase)	1.924	0.213–17.40	0.5599
LVFS (%)	(per 1 SD decrease)	1.474	0.566–3.842	0.4264
LAA eV (cm/s)	(per 1SD decrease)	4.955	0.609–39.77	0.1320
E/*E*′	(per 1SD increase)	1.099	0.126–9.599	0.9319
Fibrinogen (mg/dl)	(per 1 SD increase)	3.074	0.851–12.87	0.1011
BNP >90 pg/ml		41.39	1.280–1338	0.0358

95% CI, 95 percent confidence interval. CHADS2, an acronym for Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVFS, left ventricular percent fractional shortening; LAA eV, left atrial appendage emptying flow velocity at atrial systole; SEC, spontaneous echo contrast; *E*/*A*, the ratio of peak early to late filling velocity; *E*/*E*′, the ratio of peak early mitral annular velocity to *E* wave; BNP, brain natriuretic peptide.

reported that plasma BNP was correlated with LA/LAA dysfunction, which was evaluated by TEE in 48 patients with ischemic stroke or transient ischemic attacks (TIA) [30]. Although the study population was small, their results are consistent with those from the present study. Recently, Yukiiri et al. reported that plasma BNP was a surrogate marker for differentiating cardioembolic stroke from non-cardioembolic stroke. They also suggested that LAA eV was not a statistically significant predictor of cardioembolic stroke after adjusting for AF, plasma BNP and LA diameter [19]. However, these studies did not distinguish between cardiogenic stroke and cryptogenic stroke, which have completely different mechanisms of thromboembolism. The present results clearly demonstrated that plasma BNP levels were significantly higher in patients with cardiogenic stroke than in those with cryptogenic stroke. Therefore elevated plasma BNP levels may be a promising marker for detecting LAA dysfunction and thrombus formation in patients with acute ischemic stroke.

This study had several limitations. First, the number of patients was relatively small. Second, the patients in this study were receiving low-dose anticoagulation therapy. However, there were no significant differences in BNP, LAA eV, and the prevalence of SEC between patients with and without the therapeutic range of warfarin. Third, since we did not perform right heart catheterization during acute phase of stroke, it is possible that the patients showing low *E*/*E*′ included those with LV diastolic dysfunction.

In conclusion, high plasma BNP levels (>90 pg/ml) may be a reliable biomarker for LAA dysfunction, and may predict cardiogenic stroke but not cryptogenic stroke. Plasma BNP may be a useful non-invasive marker, in addition to the CHADS2 score, for stratification of the risk of cardioembolic stroke.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2012.02.010.

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